



Hyperbaric oxygen therapy as a complementary treatment for radiation proctitis: Useless or useful? – A literature review

Diogo Alpuim Costa, Carla Espiney Amaro, Ana Nunes, Joana Santos Cardoso, Pedro Modas Daniel, Isabel Rosa, João Vieira Branco

ORCID number: Diogo Alpuim Costa 0000-0002-1377-3032; Carla Espiney Amaro 0000-0002-2496-7027; Ana Nunes 0000-0002-0797-2342; Joana Santos Cardoso 0000-0002-8908-2318; Pedro Modas Daniel 0000-0002-4374-2472; Isabel Rosa 0000-0002-1737-7002; João Vieira Branco 0000-0001-6056-9168.

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Diogo Alpuim Costa, Department of Haematology and Oncology, CUF Oncologia, Lisboa 1998-018, Portugal

Diogo Alpuim Costa, Joana Santos Cardoso, Pedro Modas Daniel, Isabel Rosa, João Vieira Branco, Centro de Medicina Subaquática e Hiperbárica (CMSH), Portuguese Navy, Lisboa 1649-020, Portugal

Diogo Alpuim Costa, Carla Espiney Amaro, Pedro Modas Daniel, Isabel Rosa, Centro de Investigação Naval (CINAV), Portuguese Navy, Base Naval do Alfeite, Almada 2810-001, Portugal

Diogo Alpuim Costa, NOVA Medical School, Faculdade de Ciências Médicas, Lisboa 1169-056, Portugal

Carla Espiney Amaro, Department of Otorhinolaryngology, Hospital das Forças Armadas (HFAR), Lisboa 1649-020, Portugal

Ana Nunes, Department of Gastroenterology, Hospital das Forças Armadas (HFAR), Lisboa 1649-020, Portugal

Joana Santos Cardoso, Department of Vascular Surgery, Centro Hospitalar Universitário de Lisboa Central, Hospital de Santa Marta, Lisboa 1169-024, Portugal

Pedro Modas Daniel, Department of Intensive Care Unit, Hospital das Forças Armadas (HFAR), Lisboa 1649-020, Portugal

Isabel Rosa, Department of General Surgery, Hospital das Forças Armadas (HFAR), Lisboa 1649-020, Portugal

Corresponding author: Diogo Alpuim Costa, MD, Medical Assistant, Research Fellow, Department of Haematology and Oncology, CUF Oncologia, R. Mário Botas, Lisboa 1998-018, Portugal. diogoalpuimcosta@gmail.com

Abstract

Radiotherapy (RT) is the backbone of multimodality treatment of more than half of cancer cases. Despite new modern RT techniques, late complications may occur such as radiation proctitis (RP). The natural history of RP is unpredictable. Minor symptoms may resolve spontaneously or require conservative treatment. On the other hand, for similar and uncomplicated clinical contexts, symptoms may

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persist and can even be refractory to the progressive increase in treatment measures. Over the last decades, an enormous therapeutic armamentarium has been considered in RP, including hyperbaric oxygen therapy (HBOT). Currently, the evidence regarding the impact of HBOT on RP and its benefits is conflicting. Additional prospective and randomised studies are necessary to validate HBOT's effectiveness in the 'real world' clinical practice. This article reviewed the relevant literature on pathophysiology, clinical presentation, different classifications and discuss RP management including a proposal for a therapeutic algorithm with a focus on HBOT.

Key Words: Radiation proctitis; Radiation proctopathy; Radiotherapy; Radio-induced lesion; Late radiation tissue injury; Delayed radiation injury; Late sequelae; Hyperbaric oxygen therapy; Hyperbaric oxygen; Review

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Core Tip: Over the last decades, an enormous therapeutic armamentarium has been considered in radiation proctitis (RP) management including hyperbaric oxygen therapy (HBOT). However, evidence regarding the impact of HBOT on RP and its benefits is conflicting. With the lack of consensus to guide the use of HBOT for the treatment of RP, the goal of this review was to synthesise the existing data, analyse results of previous studies, identify gaps in knowledge, and discuss RP' management including a proposal of a therapeutic algorithm focusing on HBOT.

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INTRODUCTION

In recent years and on a global scale, we have witnessed a sustained increase of cancer incidence, with a steady growth rate of approximately 3% per year. According to the International Agency for Research on Cancer of the World Health Organization, it is estimated that worldwide the number of new cancers will reach almost 30 million in 2040, with a mortality of 16.5 million[1].

However, these alarming numbers may be related to the implementation of screening programs with the detection of more cases of cancer at an early stage. Moreover, the survival rates of patients diagnosed with cancer have also increased, largely due to scientific development and the commitment of health professionals in oncology. The progressive increase of this new population cancer survivors with specific clinical and social problems poses a real healthcare challenge. It is in this particular context that radio-induced lesions arise, taking into account their prevention and treatment.

In developed countries, radiotherapy (RT) is the backbone of multimodality treatment of more than half of cancer cases. Despite new modern RT techniques, delayed radiation injury can appear with a latency period of a few months to several decades. The incidence and prevalence of radio-induced lesions and their severity are not well known due to different definitions, underestimation of mild symptoms by both patients and professionals, and the imprecise notification of their appearance in clinical practice[2].

RT is a key treatment of the multimodal approach of neoplasms of the gastrointestinal and pelvic regions. The fixed anatomical position of the rectum in the pelvic brim and the proximity to the irradiated organs makes the rectum especially vulnerable to secondary ionising radiation injury[3]. Radiation proctitis (RP) or radiation proctopathy is defined as a chronic lesion of the mucosa and submucosa of the rectum or rectosigmoid transition secondary to ionising radiation[3].

Acute radio-induced lesions occur from hours or days after exposure to ionising radiation and usually resolve in less than 3 mo. On the other hand, RP is a late lesion with a median onset of 6 to 12 mo after exposure. Rare cases with a latency over 30 years have been reported. Furthermore, RT can develop a continuous process from an acute injury, where symptoms are not specific or non-existent. The clinical presumption is based on intestinal symptoms (*e.g.*, haematochezia, diarrhoea, tenesmus, abdominal pain) and in a cause-effect relationship of previous history of pelvic RT. The diagnosis can be confirmed by endoscopy with or without histologic examination, as imaging findings are usually nonspecific[4-12].

Virtually all patients will experience some clinical manifestation of acute RP during their pelvic RT treatment[8]. Previously, it was thought that only a minority of patients (5%-15%) would develop RP[9,13,14]. However, based on recent data, it is now estimated that near half of the patients may report symptoms related to RP[14,15]. Following RT, 30% of patients with prostate cancer, 12%-17% with rectal cancer, 16% with testicular cancer and 10% with cervical cancer will develop RP[16]. RP's most severe cases have an estimated 4.3%-22% incidence and a 2%-8% mortality rate[11-16].

A high risk of developing RP depends on the total radiation dose and its fractionation, the mode of application (external *vs* intracavitary), the volume of irradiated tissue and the combination of RT techniques. A cumulative dose of RT < 45 Gy is associated with a lower risk of late RT lesion in contrast to what is observed for doses > 70 Gy, for which the risk is significantly higher. The RT technique used is an essential predictor of risk for RP. Compared to brachytherapy, ionising radiation typically administered through a linear accelerator will result in greater and more significant exposure of the contiguous organs. The new RT modalities that comprise three-dimensional conformational RT, intensity-modulated RT and proton and neutron therapies seem to be associated with a lower risk of gastrointestinal toxicity[5-9,17,18].

Advanced age, low body mass index, smoking habits, previous abdominal surgery due to intraperitoneal adhesions, pelvic inflammatory disease, arterial hypertension, diabetes mellitus, previous chemotherapy, collagen and vascular diseases, xeroderma pigmentosa, Cockayne syndrome are other patient-related factors that may be associated with a higher RP risk. Among this array of risk factors, those that seem to have the most significant predictive value for RP are the history of abdominal surgery, chemotherapy, arterial hypertension, and thinness[5-13].

Although the processes of obliterating endarteritis, hypoxia, and fibrosis are already recognised as fundamental factors for their establishment and eventual evolution to chronicity, RP's pathophysiology is complex and has not yet been fully understood[12, 19-21]. This chronic condition can stabilise or gradually worsen with periods of acute inflammation.

The beneficial properties of hyperbaric oxygen, together with the growing knowledge about the pathophysiology of delayed radiation injuries, have led to the use of hyperbaric oxygen therapy (HBOT) in the treatment of RP[4]. Currently, HBOT is considered by the European Committee for Hyperbaric Medicine (ECHM) as a treatment modality for late radio-induced lesions, namely, the prevention and treatment of osteoradionecrosis of the mandible, haemorrhagic radiation cystitis and RP (degree of recommendation I/level of evidence B). Although HBOT is used in selected cases of other RT sequelae (*e.g.*, central nervous system and radio-induced laryngeal lesion), its degree and level of recommendation/evidence is lower[22].

Attending to the lack of consensus on guidelines for the use of HBOT in the treatment of RP, the goal of this review is to synthesise the existing data, analyse results of previous studies, identify gaps in knowledge, and discuss RP' management including a proposal for a therapeutic algorithm with a focus on HBOT.

RP PATHOPHYSIOLOGY

Ionising radiation can cause cellular damage, especially in mucosa with rapid renewal such as the intestinal mucosa.

Acute lesions occur predominantly in the mucosa, which consists of depletion of epithelial cells due to cytotoxicity in progenitor cells and consequent apoptosis; inflammation and infiltration of the lamina propria with polymorphonuclear leukocytes and plasma cells; eosinophilic abscesses of intestinal crypts; endothelial lesions of intestinal microvascularisation and eventual oedema of the submucosa. These processes result in mucositis that interferes with the intestinal barrier's function, allowing antigen translocation including microorganisms[23]. If the submucosa

modifications are not impactful, the epithelial cells regenerate and the process resolves spontaneously (Figure 1).

Parallel to what has been described for other late sequelae of RT, RP's pathophysiological mechanisms are not fully understood. Oxidative stress caused by reactive oxygen species (ROS) contributes to obliterating endarteritis with progressive reduction of parietal irrigation and consequent local ischaemia, formation, and diffuse progression of mucosal and submucosal fibrosis through a local proinflammatory cytokines cascade (high levels of interleukin-1 β (IL-1 β), IL-2, IL-6, IL-8, and transforming growth factor- β), which is promoted by macrophages, neutrophils, and by the differentiation of fibroblasts into myofibroblasts (Figures 1 and 2)[5,23-25]. Recently, an unique intestinal microbiota signature has been identified in an animal model of RP, which seems to be capable of increasing the expression of IL-1 β , IL-6, and tumour necrosis factor- α (Figure 2). Mice colonised with previously irradiated intestinal microbiota were more prone to RP than the control colonised with naïve intestinal microbiota[26]. Furthermore, it is postulated that the microbiota can also influence the efficacy of the cancer treatment *per se*.

This transmural pathological regenerative process of the intestinal wall will exacerbate the progressive decrease in vascular density (and consequently the formation of friable telangiectasias and lymphatic vessels dilation), cell depletion, mucosal atrophy, and stenosis of the intestinal wall. Moreover, chronic mucosal ulcers can predispose to haemorrhage, the formation of fistulae and possible risk of intestinal perforation (Figure 2)[6,8,9].

CLINICAL PRESENTATION

Clinically, RP presents itself in two forms: acute or chronic. The acute form is typically resolved within a few weeks and it is characterised by nausea, vomiting, abdominal pain, diarrhoea, urgency, tenesmus, and more rarely, lower gastrointestinal bleeding. The chronic form has a similar clinical presentation; however, it is characterised by an indelible evolution, leading, in the most severe cases, to major digestive haemorrhage, chronic constipation, faecal incontinence, severe proctalgia, stenosis, fistulisation and eventually, intestinal perforation. Moreover, patients may also have other symptoms resulting from pelvic irradiation such as radiation enteritis, haemorrhagic radiation cystitis or urethral stricture. The occurrence of colorectal neoplasms induced by radiation has also been described, mostly after a long latency period, which can be manifested by masses or non-healing ulcers[5,7,8].

For diagnosis, a cause-effect relationship should be established between the history of pelvic RT and intestinal symptoms. A rectal examination will evaluate anal sphincter tonicity and a rectosigmoidoscopy the mucosa characteristics and affected areas, excluding malignancy. Total colonoscopy can be considered to outline the true extent of the disease and/or exclude the possibility of another aetiology for colitis. Endoscopic images usually reveal a pale, friable mucosa, with telangiectasias and/or ulcerations, and a clear separation between the altered and normal region, corresponding to the irradiated zone's limit. A biopsy is usually not recommended to confirm the diagnosis because it may increase the risk of complications[7,8].

In addition, it is essential to exclude other possible causes of subacute or chronic proctitis such as inflammatory bowel disease, diverticular colitis, atherosclerotic disease or previous episodes of chronic ischemic colitis, chronic exposure to the effects of non-steroidal anti-inflammatory drugs, recent use of antibiotics that predispose to *Clostridioides difficile* infection, parasitic (e.g., amebiasis) or bacterial (e.g., *Salmonella* spp., *Campylobacter* spp.) infections due to recent travelling to endemic countries, history or risk factors for sexually transmitted diseases (e.g., *Neisseria gonorrhoeae* and herpes simplex virus) and cytomegalovirus infection in the immunocompromised patient[7,8].

In several studies, the severity of RP is objectively graded using symptom scores, such as the Radiation Proctopathy System Assessment Scale or the Late Effects Normal Tissue (LENT-SOMA) scale and considering the intraluminal findings by endoscopic grade (modified Chi grading or scales Chutkan and Gilinski). The comparison of data between studies is difficult due to the use of different severity scores. The same is true for outcome measures. Table 1 summarises some of the different classifications of RP that have been proposed in the literature[27-37].

Table 1 Classification of stages/grades of radiation proctitis

Ref.	Stages/grades	Description
Sherman[27], 1954	I-IV	Based on endoscopic findings: I: (a) Localised erythema and telangiectasia, friable mucosa with easy bleeding; no ulceration or stricture formation, and (b) More diffuse erythema along with proctitis, marked pain, and sensitivity; II: Presence of ulceration with a greyish tenacious slough, usually involving the anterior rectal wall, and proctitis with grade I lesions; III: Presence of rectovaginal fistulae or bowel perforation and varying degrees of proctitis with ulceration; IV: Presence of rectovaginal fistulae or bowel perforation and varying degrees of proctitis with ulceration.
Dean and Taylor[28], 1960	I-III	Based on clinical and endoscopic findings: I: Symptoms: Rectal bleeding, tenesmus, sphincter instability, mucoid discharge; endoscopic findings of vascular congestion, friability of the mucosa, mucosal thickening, mucoid discharge; II: Same symptoms as before; endoscopic findings of ulcerations, underlying thrombosis of the small vessels; III: Same symptoms as before plus perineal sepsis, incontinence, diarrhoea, perianal purulent discharge; endoscopic findings of necrosis, fistulae, strictures.
Gilinsky <i>et al</i> [29], 1983	Normal; Mild; Moderate; Severe	Based on endoscopic findings: Score 0: Normal mucosa; Score 3: Erythema and/or telangiectasia, oedema, thickening, pallor of mucosa; Score 6: Friability; Score 9: Ulceration and/or necrosis.
Langberg <i>et al</i> [30], 1992	1-3	Based on histopathologic findings: Thickening of serosa: (1) Slight thickening of serosa, hyperplasia of peritoneal mesothelium; and (2) Marked thickening of serosa; and (3) Extreme thickening and fibrosis serosa. Mucosal alterations: (1) Small superficial ulcerations; and (2) Ulcerations involving more than half of the intestinal circumference. Epithelial atypia: (1) Abnormally oriented crypts; (2) Irregular crypt regeneration with atypical epithelial cells; and (3) Adenocarcinoma. Vascular sclerosis: (1) Slight double normal thickness, broadened and hyalinised collagen fibres; (2) Submucosa three to four times normal thickness, abnormal collagen fibres; and (3) Massive fibrosis including muscularis. Lymph congestion: (1) Dilated lymph vessels or cystic collections of lymph. Ileitis cystica profunda: (1) Submucosal glandular inclusions; (2) Submucosal cysts with polypoid elevation of the mucosa; and (3) Large cysts extending into the muscularis.
Chutkan <i>et al</i> [31], 1997	0-4	Based on clinical findings: 0: No haemorrhage; 1: Blood on toilet paper or mixed with faeces; 2: Drops of blood in the toilet; 3: Severe haemorrhage with expulsion of clots; 4: Haemorrhage that requires transfusion.
Wachter <i>et al</i> [32], 2000. Vienna Rectoscopy Score	0-5	Based on endoscopic findings: Score 0: Congested mucosa (grade 1); Score 1: Congested mucosa (grade 2), telangiectasia (grade 1); Score 2: Congested mucosa (grade 3), telangiectasia (grade 2); Score 3: Congested mucosa (any grade), telangiectasia (grade 3), ulceration (grade 1); Score 4: Congested mucosa (any grade), telangiectasia (any grade), ulceration (grade 2), stricture (grade 1); Score 5: Congested mucosa (any grade), telangiectasia (any grade), ulceration (grade 3), stricture (grade 2), necrosis (any grade).
Zinicola <i>et al</i> [33], 2003. Bleeding Scale for Radiation-Induced Haemorrhagic Proctitis	0-4	Based on clinical findings: 0: No bleeding; 1: Intermittent bleeding (once weekly or less); 2: Persistent bleeding (twice or more weekly); 3: Daily bleeding or anaemia; 4: Require blood transfusion.
Chi <i>et al</i> [34], 2005. RTD grading scale	0-3	Based on RTD endoscopic findings: 0: Normal mucosa; 1: < 10 telangiectasias; 2: > 10 telangiectasias; 3: Confluent lesions, active bleeding or friable mucosa.
Ehrenpreis <i>et al</i> [35], 2005. Radiation Proctopathy System Assessment Scale (RPSAS)	1-5	Based on clinical findings: Diarrhoea. Urgency. Rectal pain. Tenesmus. Rectal bleeding. Faecal incontinence. Severity: 1: No problem. 2: Mild problem—can be ignored when you do not think about it. 3: Moderate problem—cannot be ignored; no effect on ADL. 4: Severe problem—influences your concentration on ADL. 5: Very severe problem—markedly influences your ADL and/or requires rest. Frequency: 1: Monthly; 2: Weekly; 3: Several times <i>per week</i> ; 4: Daily; 5: Throughout the day.
Cox <i>et al</i> [36], 1995. Late Radiation Morbidity Scoring Criteria Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer	0-5. Late (> 3 mo)	Based on clinical and imaging findings: 0: No changes; 1: Mild diarrhoea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding; 2: Moderate diarrhoea or colic, bowel movement > 5 times daily, excessive rectal mucus or intermittent bleeding; 3: Obstruction or bleeding requiring surgery; 4: Necrosis, perforation, or fistulae; 5: Death related to adverse event.
NCI CTCAE version 5.0[37], 2017	1-5	Based on clinical findings: 1: Mild adverse event; rectal discomfort, intervention not indicated; 2: Moderate adverse event; rectal discomfort, passing blood or mucus, medical intervention indicated, limiting instrumental ADL; 3: Severe and undesirable adverse event, faecal urgency or stool incontinence, limiting self-care ADL; 4: Life-threatening or disabling adverse event, urgent intervention needed; 5: Death related to adverse event.

ADL: Activities of daily living; RTD: Rectal telangiectasia density.

RP TREATMENT

The treatment of acute RP is essentially symptomatic and in accordance with the guidelines for the treatment of mucositis of other aetiologies[38,39]. In the absence of response to first-line antidiarrheal medication, it must be recommended treatment with octreotide or other somatostatin analogues and butyrate enemas that seem to accelerate the intestinal mucosa regeneration process. There is clinical evidence that

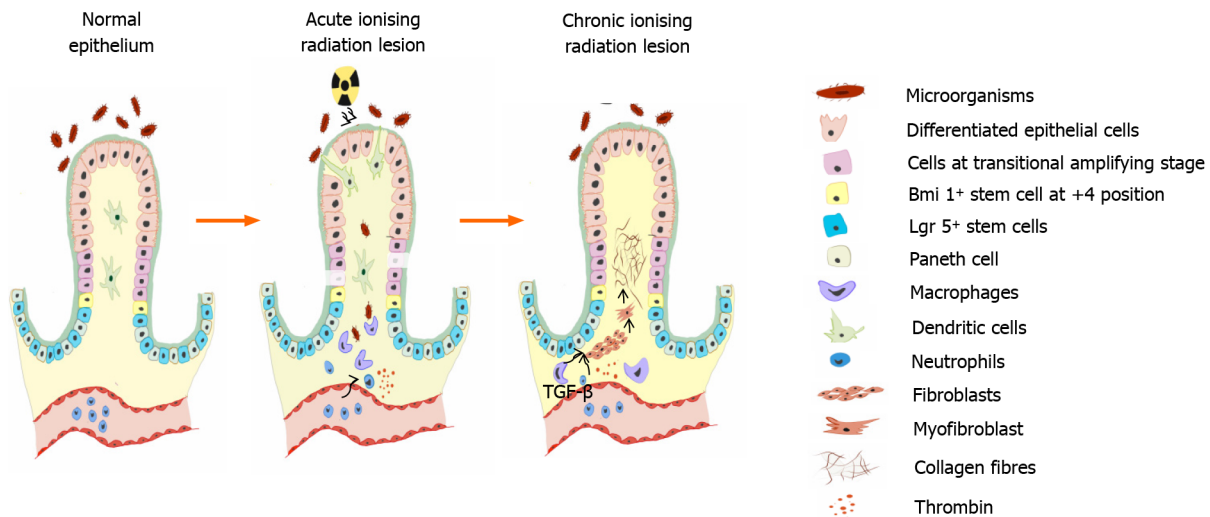


Figure 1 Representative scheme of intestinal injury induced by ionising radiation. In a healthy gut, crypts are with intact mucosa. Lgr5⁺ stem cells proliferate and cells migrate upwards to provide differentiated epithelial cells of the villi. Acute lesions occur predominantly through different pathological processes: Depletion of epithelial cells due to cytotoxicity in progenitor cells and consequent apoptosis; inflammation and infiltration of the lamina propria with polymorphonuclear leukocytes and plasma cells; eosinophilic abscesses of intestinal crypts; endothelial lesions of intestinal microvascularisation with the release of thrombin and eventual oedema of the submucosa; influx of antigenic material, including gut microbiota into the lamina propria. If the submucosa modifications are not impactful, the epithelial cells regenerate, and the process resolves spontaneously. The constitutive and chronic phase comprises obliterating endarteritis with progressive reduction of parietal irrigation and consequent local ischaemia; formation and diffuse progression of mucosal and submucosal fibrosis through a local proinflammatory cytokine cascade (high levels of interleukin-1 β (IL-1 β), IL-2, IL-6, IL-8, and transforming growth factor- β), which is promoted by macrophages, neutrophils and by the differentiation of fibroblasts into myofibroblasts. Citation: Adapted from Costa *et al*[21] and Kumagai *et al*[23].

intrarectal amifostine (ROS scavenger) could be, in selected patients, a possible protective pharmacological measure against the acute effects of RT. Generally, the acute RP is a self-limiting situation, although in about 20% of cases, it is necessary to suspend or even interrupt RT treatments[7,38,39].

The natural history of RP *per se* is unpredictable. Minor symptoms may resolve spontaneously or require conservative treatment. On the other hand, symptoms may persist for similar and uncomplicated clinical contexts and become refractory to the progressive increase in therapeutic intervention. Thus, early diagnosis and intervention are essential and symptoms should not be overlooked, even if they have little impact on the patient's quality of life (QoL).

The management of RP can be challenging and requires a holistic approach for which there is no gold standard protocol. Furthermore, there are no prophylactic measures that have been shown to be beneficial in reducing RP incidence. Concerning treatment options, most of the clinical evidence is based on case studies and small series. Therapeutic management should be personalised according to the patient, the severity of the clinical condition, and the institution's experience. The non-invasive or minimally invasive measures include changing the diet and symptom control with pharmacological and endoscopic support. In terms of medical treatment, the intrarectal application of formalin (4%-10% formaldehyde) and sucralfate enemas stand out as effective measures to control bleeding in patients with haemorrhagic RP. Studies present conflicting results for the use of short-chain fatty acid enemas. There is a lack of scientific evidence to recommend the use of alternative treatments such as mesalamine, ozone therapy, metronidazole, vitamin A, antioxidant vitamin complexes (vitamin C and E) and pentoxifylline. Endoscopic treatment with plasma argon has been effective in controlling and treating lower gastrointestinal bleeding. Endoscopic bipolar electrocoagulation, radiofrequency ablation, Nd: YAG laser and cryotherapy are possible alternatives to argon, although their evidence level is low. Despite the enormous therapeutic armamentarium, the more severe RP cases may require radiological intervention for lower gastrointestinal bleeding and surgical intervention, especially in complications such as effective control of lower gastrointestinal bleeding, fistulisation, occlusion, and intestinal perforation[3,5,7,8,38,39].

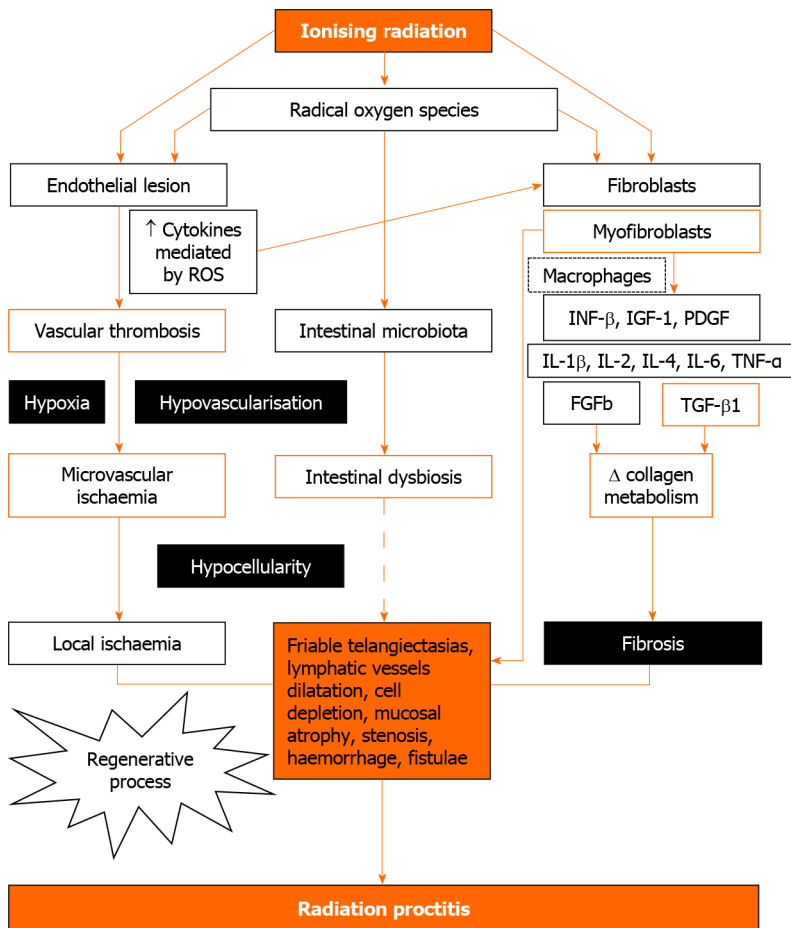


Figure 2 Representative scheme of the several pathophysiological mechanisms involved in radiation proctitis: The hypoxia/hypocellularity/hypovascularisation, intestinal microbiota and the fibroatrophic theories. FGFb: Basic fibroblast growth factor; IGF1: Insulin-like growth factor 1; IL: Interleukin; INF-β: Interferon- beta; PDGF: Platelet-derived growth factor; ROS: Reactive oxygen species; TGF-β1: Transforming growth factor beta-1; TNF-α: Tumour necrosis factor-alpha. Citation: Adapted from Costa DA *et al*[21].

HBOT

HBOT is a treatment based on the inhalation of pure oxygen (100%) in an environment with an atmospheric pressure higher than that existing at sea level (1 atmosphere absolute [ATA]). The HBOT sessions are held inside hermetically sealed hyperbaric chambers, classified as type IIb medical devices (directive 93/42 ECC of June 14, 1993, concerning medical devices). HBOT is used in several clinical conditions as well as in professional and military training. Therapeutic HBOT usually involves pressures higher than 1.4 ATA (141.8 kPa), most frequently ranging between 2.0 (202.6 kPa) and 2.5 ATA (253.3 kPa) for 60 to 120 min[40].

Currently, the ECHM recommends HBOT for the treatment of RP (degree of recommendation I/ level of evidence B)[22]. Unlike most conventional treatment that only alleviated symptoms, HBOT can favourably change the natural history of other RT late sequelae[4]. Its clinical benefit emanates from the therapeutic effects of hyperbaric oxygen that include, among others, the promotion of tissue oxygenation, neovascularisation, reepithelialisation, and the reversal of the fibroatrophic process induced by ionising radiation[16,21,41,42].

The mechanisms that result in HBOT beneficial effects can also cause side effects in some patients, primarily due to pressure and oxygen toxicity. However, when appropriate therapeutics protocols are applied, HBOT is a safe and low-risk intervention, with the adverse events being infrequent and typically not severe[40-43].

In 1991, Charneau *et al*[44] treated the first RP patient with HBOT. The 74-year-old patient had a 5-mo history of transfusion-dependent haemorrhagic RP. For this patient, after the failure of previous treatments (enema with corticosteroids and Nd: YAG laser), HBOT was considered a strategy to avoid surgery. After 82 sessions of HBOT (2.5 ATA, for 90 min, twice daily), a complete clinical response was observed, which remained during the follow-up period of at least 9 mo. After this pioneering

report, others were published, including case reports, retrospective, (non)-randomised studies and clinical trials, as well as several reviews and meta-analyses that studied the clinical impact of HBOT on RP (Table 2)[16,45-71]. However, most studies had both a small number of cases treated and a short follow-up period.

In 1997, Warren *et al*[47] conducted a study with 14 patients undergoing two pressurisation regimens ($n = 9$; 2 ATA, for 120 min, 5-6 times per week; $n = 5$; 2.35 ATA, for 90 min, 5 times per week). The authors documented an overall response rate of 64.3% (57.1% with complete responses) for an average follow-up period of 14.6 (range 2-35) mo. In the same year, Woo *et al*[48], published a study with 18 patients submitted to 24 sessions of HBOT (2 ATA, for 105 min, 6 times per week) with a follow-up period of 14 (range 3-65) mo. In this study, different response rates were reported according to the symptoms analysed: Haemorrhage 41.2% (7/17); rectal pain 50% (2/4); incontinence 75% (3/4) and diarrhoea 50% (4/8). Furthermore, most patients (77.7%) had already undergone other treatments but with little clinical benefit ($n = 13$, enema with corticosteroids; $n = 1$, formalin). Gouëlle *et al*[52], published a study with 36 patients submitted to an average of 67 sessions of HBOT (2.5 ATA, for 90 min, 5 times per week). An overall response rate of 53% (19/36) was observed immediately after the end of the treatment. In the 52-mo follow-up period, the overall response rate was 66% (21/32). In 2002, in a systematic review published by Feldmeier and Hampson[2], 14 publications were evaluated in the context of RP and radiation enteritis (12 studies in humans and 2 in animals). Of the 9 studies, 114 patients were considered, and an overall response rate of 95.6% was documented (36%, 41 patients with complete response; 60%, 68 patients with better symptomatic control). Despite these studies have shown an improvement in RP with HBOT, a clinical benefit has also been verified in the small intestine radio-induced malabsorption syndrome. In 2007, Marshall *et al*[16], published the largest study carried out up to that time, with 65 patients with enteritis and RP (85% of patients). The authors described an overall response rate of 68% (43% with complete responses) after at least 30 sessions of HBOT (2.4 ATA, for 90 min, 5 times per week). However, half of the patients (49.2%, 32) had to be submitted to more HBOT sessions, up to a maximum of 60, due to partial response or recurrence of symptoms. The mean follow-up time was 23 (range 1-70) mo. The response rate of patients with low gastrointestinal bleeding was 70%. In those dependent on transfusions, the response rate was very satisfactory since 75% of these patients no longer needed transfusion support. For symptoms other than haemorrhage, the response rate was 58%, with pain reduction, nutritional status improvement, intestinal transit regularisation and even fistulae closure. Moreover, no correlation was established between the treatment response rate and the duration of symptoms or the time between RT and initiation of HBOT.

In 2008, Clarke *et al*[65] published the results of the first multicentre, randomised, sham-controlled, double-blind clinical trial (HORTIS) that included patients with RP refractory to other therapeutic interventions. A total of 150 patients were enrolled, but only 120 completed the study. Patients were randomised to HBOT (Group 1: 2.0 ATA, for 90 min, 5 times per week) or sham treatment with 21% oxygen (Group 2: 1.34-1.1 ATA, for 90 min, 5 times per week). The clinical response evaluation was performed after 30 treatment sessions, with the possibility of 10 additional sessions, depending on the investigator's decision. Only 3 patients did not accept the crossover to the active arm of the initial HBOT (Group 1). After adjusting covariates and for an average follow-up period of 2 years, Group 1 significantly improved the mean LENT-SOMA score (5.00 *vs* 2.61, $P = 0.0019$). In the initial allocation phase and after the first efficacy assessment, the experimental group's overall response rate was higher than in the control group (88.9% *vs* 62.5%, $P = 0.0009$). Furthermore, there was also a significant improvement in QoL (pattern of pain, bleeding and intestinal transit) in Group 1 (including in the crossover subgroup of patients). It is noteworthy that, for Group 1, the improvement in QoL in terms of faecal incontinence, faecal urgency, pain and intestinal transit was consistent throughout the follow-up period. In 2015, Tahir *et al* [69] reported an overall response rate of 95% in the 59 patients treated with RP (51% of patients with complete response for a median duration of 15 mo). Bennett *et al*[72], in a Cochrane meta-analysis published in 2016, documented a significant increase in the clinical improvement or even remission of RP after HBOT (relative risk 1.72; 95% confidence interval 1.0-2.9, $P = 0.04$, NNT to benefit 5).

In 2016, Glover *et al*[70], in a multicentre, randomised, double-blind, sham-controlled phase 3 trial (HOT2), evaluated the clinical benefit of HBOT in patients with chronic bowel dysfunction after RT in the context of pelvic neoplasms. Treatment efficacy was determined by comparing the Inflammatory Bowel Disease Questionnaire (IBDQ) and the IBDQ rectal bleeding scores assessed before and 12 mo after starting treatment. Moreover, other secondary endpoints were evaluated: LENT-SOMA, the

Table 2 Summary of the case-series or clinical trials described in the literature regarding the use of hyperbaric oxygen therapy in the treatment of radiation proctitis

Ref.	Study design	Patients (n)	RP stages/grades, patients (n)	Other (previous) treatments (%)	HBOT protocol	N° sessions	Overall response rate (%)	Complete response (%)	Follow-up period (mo)
Bouachour <i>et al</i> [45], 1990	Retrospective	8	NA	100%	2.5 ATA, 90 min, twice daily (4 wk)-> Once daily	80 ± 10	87.5%	75%	[4-20]
Feldmeier <i>et al</i> [46], 1996	Retrospective	7	RTOG/EORTC[36]: 4	28.6%	2.4 ATA, 90 min, 5 ×/wk	24 [3-50]	57%	57%	NA
Warren <i>et al</i> [47], 1997	Retrospective	14	Bleeding (n = 11); Diarrhoea (n = 5); Rectal pain (n = 4); Tenesmus (n = 2)	78.6%	2.0 ATA, 120 min, 5-6/wk; 2.35 ATA, 90 min, 5 ×/wk	39 [20-72]	64.3%	57.1%	14.6 [2-35]
Woo <i>et al</i> [48], 1997	Retrospective	18	Bleeding (n = 17); Diarrhoea (n = 8); Rectal pain (n = 4); Incontinence (n = 4)	77.7%	2.0 ATA, 105 min, 6 ×/wk	24 [40]	55.5%; Incontinence 75%; Diarrhoea 50%; Rectal pain 50%; Haemorrhage 41.2%	11.1%; 50%; 25%; 23.5%	14 [65]
Bredfeldt and Hampson [49], 1998	Retrospective	19	NA	NA	2.36 ATA, 90 min, 5 ×/wk	30	84%	47%	NA
Ugheoke <i>et al</i> [50], 1998	Retrospective	8	NA	NA	2.5 ATA, 90 min, 5 ×/wk	28 [20-40]	62.5%	NA	NA
Carl <i>et al</i> [51], 1998	Retrospective	2	Bleeding (n = 1); Rectal pain (n = 1)	NA	2.4 ATA, 90 min, 5 ×/wk	38, 40	50%	50%	NA
Gouëllou <i>et al</i> [52], 1999	Retrospective	36	LENT-SOMA: Grade 1 (n = 1); Grade 2 (n = 11); Grade 3 (n = 16); Grade 4 (n = 8)	NA	2.5 ATA, 90 min, 5 ×/wk	67 (mean)	66%	25%	52
Kitta <i>et al</i> [53], 2000	Retrospective	4	Bleeding (n = 3); Rectal pain (n = 1)	100%	2.0 ATA, 60 min, 5 ×/wk	37.5 [30-60]	75%	25%	NA
Bem <i>et al</i> [54], 2000	Retrospective	2	Dean and Taylor [28]: I-II	100%	2.4 ATA, 90 min, 5 ×/wk	60, 60	100%	100%	[3-48]
Roque <i>et al</i> [55], 2001	Retrospective	6	NA	NA	2.5 ATA, 90 min, 5 ×/wk	37 [20-60]	85%	NA	NA
Mayer <i>et al</i> [56], 2001	Retrospective	10	RTOG/EORTC[36]: Grade 2 (n = 4); Grade 3 (n = 6)	Majority (%) not stated)	2.2-2.4 ATA, 60 min, 7 ×/wk	28 [13-60]	90%	30%	15.3 [7.5-26.9]
Boyle <i>et al</i> [57], 2002	Retrospective	19	NA	NA	2.0 ATA, 120 min, 5 ×/wk	59 [27-80]	68%	NA	NA
Jones <i>et al</i> [58], 2006	Retrospective	10	LENT-SOMA: Grade 2 (n = 7); Grade 3 (n = 3)	100%	2.0-2.5, 90 min, 5 ×/wk	40 [36-41]	77%; Haemorrhage 88.8%; Diarrhoea 80%; Rectal pain 80%	44.4%; 60%; 20%	25 [6-43]
Dall'Era <i>et al</i> [59], 2006	Retrospective	27	RTOG/EORTC[36]: 3-4	100%	2.4 ATA, 90 min, 7-7 ×/wk	36 [29-60]	66.6%; Haemorrhage 76%; Rectal pain 75%; Faecal urgency 75%; Rectal ulcer 50%	37%; 48%; 0%; 50%; 21%	13 [1-60]
Fink <i>et al</i> [60], 2006	Retrospective	4	NA	100%	2.4 ATA, 90 min, 5 ×/wk	31 [28-37]	75%	25%	33
Girnius <i>et al</i> [61], 2006	Retrospective	9	Bleeding Scale for Radiation-Induced	100%	2.5 ATA, 90 min, 5 ×/wk	58 [22-80]	100%	77.7%	17 [1-77]

			Haemorrhagic Proctitis[33]: Grade 2 (<i>n</i> = 1); Grade 3 (<i>n</i> = 3); Grade 4 (<i>n</i> = 5)						
Marshall <i>et al</i> [16], 2007	Retrospective	65 (15 with lesions beyond the rectum)	Bleeding (<i>n</i> = 54); Diarrhoea (<i>n</i> = 25); Rectal pain (<i>n</i> = 25); Tenesmus, urgency, incontinence (<i>n</i> = 13); Malnutrition, weight loss (<i>n</i> = 7); Bloating, cramping (<i>n</i> = 6); Nausea, emesis (<i>n</i> = 5); Fistulae (<i>n</i> = 2); Total parenteral nutrition (<i>n</i> = 2)	65%	2.36 ATA, 90 min, 5 ×/wk	30-> If partial response-> 60	68% (all patients); 65% (rectum); 73% (proximal sites); Haemorrhage 70%; Other symptoms 58% (including pain relief, improved nutritional status and intestinal transit, closure of fistulae)	43%; 39%; 60%; 75%; 33%	23 [1-70]
Sidik <i>et al</i> [62,63], 2007	Prospective, randomised clinical trial	HBOT 32; Comparator33	LENT-SOMA: HBOT, mean 7.7 ± 2.0; Control, mean 6.8 ± 2.3. Karnofsky scale: HBOT, mean 73.8 ± 6; Control, mean 74.6 ± 8.3	NA	HBOT, Protocol not reported <i>vs</i> Comparator described as “symptomatic treatment”	HBOT, Minimum 18 sessions	Outcomes poorly reported (losses to follow-up, not all patient data provided)	NA	6
Safra <i>et al</i> [64], 2008	Retrospective	6	NCI CTCAE[37]: Mean 3.3 [2-4]	100%	2.0 ATA, 90 min, 7 ×/wk	27 [16-40]. Not only RP	100%	16.7%	NA
Clarke <i>et al</i> [65], 2008	Randomised, double-blind, sham-controlled, crossover allowed (“HORTIS”)	HBOT 76; Comparator74	LENT-SOMA: HBOT, mean 12.55; Sham, mean 12.84	100%	HBOT, 2.0 ATA, 90 min, 5 ×/wk <i>vs</i> Sham treatment 1.34- > 1.1 ATA O ₂ 21%, 90 min, 5 ×/wk	30-> 40	HBOT: 88.9%. Improved bowel-specific and bowel bother and function QoL scores (before crossover) <i>vs</i> Sham treatment: 62.5%	HBOT: 7.9% <i>vs</i> Sham: 0%	25 [12-60]
Alvaro-Villegas <i>et al</i> [66], 2011	Prospective, non-randomised clinical trial	HBOT 17; Comparator14	LENT-SOMA: HBOT, 12.1 ± 2.9; APC, 13.3 ± 2.9	NA	HBOT 2.0-2.5 ATA, 90 min, 5 ×/wk <i>vs</i> Non-contact APC, 2.3 mm diameter catheter, 1.6 L/min flow rate at 60 W, mean 3 ± 1 (SD) sessions	HBOT, 35 ± 5 <i>vs</i> APC, 3 ± 1	HBOT: 82% <i>vs</i> APC: 87%	NA	3
Oliai <i>et al</i> [67], 2012	Retrospective	4	LENT-SOMA: Mean 0.66 [0.36-0.93]. Severity of rectal bleeding: Persistent (<i>n</i> = 3), Occasional (<i>n</i> = 1)	100%	2.0 ATA, 90-105 min, 5 ×/wk	37.5 [30-40]	75%	50%	NA
Carvalho <i>et al</i> [68], 2014	Retrospective	30	NA	NA	2.5 ATA, 100 min, 5 ×/wk	66 [38-80]	96.7%	73.3%	NA
Tahir <i>et al</i> [69], 2015	Retrospective	59	NA	NA	2.4 ATA, 70 min, 7x/wk	NA	95%	51%	Major response 15 [2-76]. Minor response 20 [1-84]
Glover <i>et al</i> [70], 2016	Randomised, double-blind, sham-controlled phase 3 clinical trial (“HOT2”)	Ratio 2:1; HBOT 55; Comparator29	LENT-SOMA: Grade 2; Grade 1 with intermittent symptoms. IBDQ bowel function component (n/IQR): HBOT 48 (42-52); Sham 51 (44-59). IBDQ rectal	100%	HBOT 2.4 ATA, 90 min, 5 ×/wk <i>vs</i> Sham treatment 1.34 ATA O ₂ 21%, 90 min, 5 ×/wk	40 (89% of patients) < 38 (11% of patients)	HBOT: IBDQ bowel function component (n/IQR): Δ 3.5 (-3-11). IBDQ rectal bleeding (n/IQR): Δ 3 (1-3) <i>vs</i> Sham treatment: IBDQ	NA	13.2 [12.4-14.2]

			bleeding (n/IQR): HBOT 3 (2-4); Sham 3 (2-4). NCI CTCAE [64]: Grade 1-3, 46 (55%). EORTC QLQ-CR38 Question 59: Grade 1-3, 47 (59%)				bowel function component (n/IQR): Δ 4 (-6- 9); IBDQ rectal bleeding (n/IQR): Δ 1 (1- 2)		
Yoshimizu <i>et al</i> [71], 2017	Retrospective	5	Sherman[27]: Grade II ($n = 3$); Grade III ($n = 1$); Grade IV ($n = 1$)	NA	2.5 ATA, 60 min, 5 \times /wk	76 [40- 100]	100%	20%	NA

APC: Argon plasma coagulation; ATA: Atmosphere absolute; HBOT: Hyperbaric oxygen therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; IQR: Interquartile range; min, minute; NA: Not available or not applicable; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; O₂: Oxygen; QoL: Quality of life; RP: Radiation proctitis; SD: Standard deviation; Δ : Median change from baseline to 12 mo.

11-question questionnaire related to symptoms selected from the CTCAE gastrointestinal scale (version 4.0) and QoL through validated questionnaires (Questionnaire basic EORTC QLQ-C30 and colorectal module QLQ-CR38). Patients of both sexes with ages over 18 years were included, with at least grade 2 gastrointestinal symptoms of any category of LENT-SOMA or grade 1 with intermittent symptoms due to RT performed at least 12 mo before in the context of rectal, prostate, testicle, bladder, cervix, vagina, vulva or ovary neoplasms. Patients with grade 3 symptoms LENT-SOMA were excluded since they have higher affection on activities of daily living and require, generally, more aggressive treatments. Patients with RT symptoms were considered eligible for the trial only if they had been submitted to other general interventions for at least 3 mo (*e.g.*, diet change, oral therapeutic optimisation) with no improvement. Patients were randomised in a 2:1 ratio in favour of HBOT and stratified by centre. Patients were randomised to HBOT (2.4 ATA, for 90 min, 5 times per week) or 21% oxygen (1.3 ATA, for 90 min, 5 times per week). Of the 84 patients included in this clinical trial, 55 underwent HBOT and 29 sham treatment. In the analysis of clinical efficacy, no difference was identified between the two arms, when comparing the main endpoints: IBDQ bowel component [HBOT = 46; sham treatment = 23; HBOT: 4 (-3 to 11) *vs* sham treatment: 4 (-6 to 9), $P = 0.50$] and IBDQ rectal bleeding [HBOT = 29; sham treatment = 11; HBOT: 3 (1 to 3) *vs* sham treatment: 1 (1 to 2), $P = 0.092$].

The results of the HOT2 clinical trial are inconsistent with most previous clinical evidence, including the Cochrane meta-analysis[72], primarily based on the HORTIS [65] clinical trial. The HOT2 study[70] is a very relevant clinical trial from a methodological point of view: Phase 3, randomisation 2:1, stratification by centre, double-blind, sham-controlled, with primary and secondary endpoints with previously validated scores and questionnaires and with well-defined inclusion/exclusion criteria, including a period of at least 3 mo for possible symptom optimisation and control. However, one can enumerate some aspects that can be criticised (not only exclusively for this trial): (1) The sample size is debatable for a phase 3 clinical trial when it is supposed to comprises a total number of patients over 300. The statistical calculation was based on assumptions defined and validated in previous studies. However, the comparison between the two arms was performed with an insufficient number of patients (HBOT: 46 *vs* sham treatment: 23); (2) The drop-out rate was 17.86% (15 patients: 9 from the HBOT group and 6 from sham treatment), with only 69 out of 84 patients having a 12-mo follow-up period. The final statistical power was 75%, although the study had been designed for 80% power; (3) Patients with symptoms \geq grade 3 LENT-SOMA (*e.g.*, severe faecal incontinence or transfusion-dependent RP) were not included. Thus, one cannot generalise the results for this subgroup; (4) It is unknown whether the percentage of patients with a medical history of lower gastrointestinal bleeding influences their progress during the study (HBOT: 62% *vs* sham treatment: 79%); (5) The dietary and/or pharmacological measures performed in the period prior to randomisation were not discriminated (*e.g.*, diet type, probiotics, antibiotic cycles). Did these different procedures influence the natural history of the disease and the potential response to treatment? (6) The smoking habits of the patients were not quantified. Otto *et al*[73], in a study on diabetic foot, determined that patients with above a 10 pack-year (P-Y) history of smoking would need an average of more than 8 to 14 sessions of HBOT to obtain the same therapeutic effect as non-smokers. Freiburger *et al*[74] reported that in patients with mandible osteoradionecrosis, those who smoked showed a shorter maintained treatment period response to HBOT when compared to non-smoking patients (15.8 *vs* 86.1 mo). The stratification by smoking

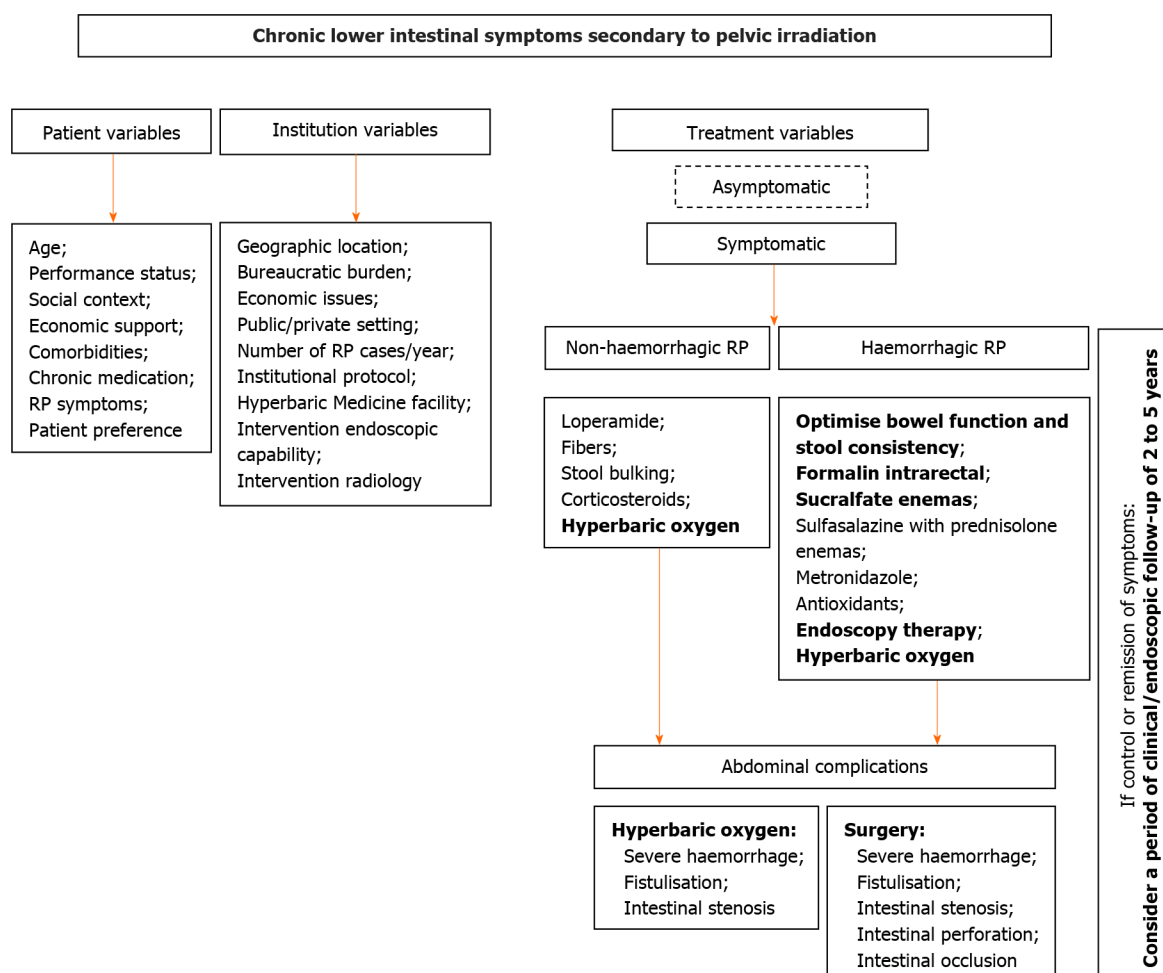


Figure 3 Suggested treatment algorithm for radiation proctitis based on variables related to the patient, institution, and the severity of the clinical context. RP: Radiation proctitis; RT: Radiotherapy.

habits could have been relevant in this trial (non-smoker or smoker ≤ 10 P-Y *vs* > 10 P-Y); (7) The distribution of the subgroup of patients ($n = 9$; 11%) who did not complete the 40 treatment sessions in both arms of the clinical trial is unknown; (8) The endoscopic response to the recommended treatments is unknown; (9) The clinical and endoscopic evolution beyond the median follow-up period 13.2 (range 12.4-14.2) is also unknown. In HORTIS clinical trial[65] it was observed and additional and maintained response beyond 12 mo of the follow-up period; and (10) The absence of a third arm in the study comparing HBOT to another conventional treatment for RP.

We recommend that HBOT, combined with nutritional support and local treatment, may be beneficial for patients with moderate to severe symptoms that do not require surgical intervention. The HBOT regimen should include at least 20-30 sessions with a pressure of 2 to 2.5 ATA for 60 to 120 min/d to ensure a more effective clinical response. The treatment protocol total duration may be extended to several weeks until a clinical and radiological complete response is obtained, and the follow-up should be personalised to each clinical context, considering a period of 2 to 5 years (Figure 3).

CONCLUSION

Although there are several effective therapeutic strategies to treat RP and improve its clinical condition, gold standard management has not yet been established. RP's management approach must be personalised according to the patient, clinical condition severity, and the institution's experience. The most conservative treatment comprises diet modulation and nutritional support, oral and intrarectal pharmacological treatment and HBOT. Endoscopic treatment may be indicated for the control and treatment of lower gastrointestinal bleeding. In severe refractory disease with

complications, surgical intervention should be considered.

During HBOT, the occurrence of adverse events is relatively infrequent. HBOT may potentially alleviate gastrointestinal radio-induced complications, including rectal bleeding, diarrhoea and pain. The authors' expectancies are that, in the near future, the controversy regarding HBOT in RP will be dimmed. More prospective and randomised studies are needed to validate the effectiveness of HBOT in the 'real-world' clinical practice.

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